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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/018,695	06/26/2002	Nathalie Garcon	B45186	7784
20462	7590	11/15/2006	EXAMINER PARKIN, JEFFREY S	
SMITHKLINE BEECHAM CORPORATION CORPORATE INTELLECTUAL PROPERTY-US, UW2220 P. O. BOX 1539 KING OF PRUSSIA, PA 19406-0939			ART UNIT 1648	PAPER NUMBER

DATE MAILED: 11/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/018,695	GARCON ET AL.
	Examiner	Art Unit
	Jeffrey S. Parkin, Ph.D.	1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 03 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 09/22/2004; 01/21/2005.

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 15-29 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 15-29 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on 13 December 2001 is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 12/13/2001.

4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.

5) Notice of Informal Patent Application

6) Other: _____.

Detailed Office Action

Status of the Claims

Acknowledgement is hereby made of receipt and entry of the communications filed 21 January, 2005, and 22 September, 2004. Claims 15-29 are pending in the instant application. Applicants' election of Group I (claims 15-29) is acknowledged. Because applicant did not distinctly and specifically point out the purported errors in the restriction requirement, the election has been treated as an election without traverse (refer to M.P.E.P. § 818.03(a)).

37 C.F.R. § 1.98

The information disclosure statement filed 13 December, 2001, has been placed in the application file and the information referred to therein has been considered. Applicants are reminded that the listing of references in the specification is not a proper information disclosure statement. 37 C.F.R. § 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and M.P.E.P. § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited or considered by the examiner on a form PTO-892 or PTO-1449, they have not been considered.

35 U.S.C. § 112, Second Paragraph

Claims 15-29 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant

regards as the invention. Two separate requirements are set forth under this statute: (1) the claims must set forth the subject matter that applicants regard as their invention; and (2) the claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant. Claims 15, 16, and 25-29 all contain the abbreviation HIV. First, to avoid confusion or ambiguity in the art, the full term should be employed prior to the use of an abbreviation (i.e., a human immunodeficiency virus (HIV) antigen). Second, the term HIV could potentially encompass HIV-1, -2, or both -1 and -2. The indiscriminate use of this term frequently leads to confusion in terms of ascertaining the actual metes and bounds of the patent protection desired. The disclosure appears to be directed toward HIV-1 vaccine compositions, not HIV-2 or both HIV-1 and -2. Appropriate clarification is required.

Claim 16 contains the phrase "immunologically equivalent derivatives thereof" which is vague and indefinite since it fails to set forth any meaningful structural criteria. What constitutes an immunologically equivalent antigen? Which immunological properties (i.e., induction of humoral, CD4⁺, CD8⁺, etc.) are encompassed by the claim language? What are the common molecular determinants modulating these interactions? Appropriate correction is required.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it

is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 25-29 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 25-27 and 29 are directed toward methods for the prevention or amelioration of HIV infection through the administration of a composition comprising an HIV antigen and CpG oligonucleotide. Claim 28 is directed toward a method for the production of a vaccine comprising an HIV antigen and CpG immunostimulatory oligonucleotide.

The legal considerations that govern enablement determinations pertaining to undue experimentation have been clearly set forth. *Enzo Biochem, Inc.*, 52 U.S.P.Q.2d 1129 (C.A.F.C. 1999). *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988). *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

Unpredictability of the Art

To date, there is no effective HIV vaccine. Several vaccines have undergone preliminary clinical trials and none have generated protective or therapeutic immune responses. This is not surprising since the correlates of human protection remain to be elucidated. Accordingly, the skilled artisan cannot begin to ascertain which immunogens, adjuvants, and immunization regimens will provide the desired immune response. Moreover, the *quasispecies* nature and high viral burden associated with HIV infection lead to immune evasion and escape. Finally, there are no animal models that are reasonably predictive of vaccine efficacy (Haynes, 1996; Piguet et al., 2001; Staprans et al., 2004; Gallo, 2005).¹²³⁴

Absence of Working Examples

Considering the unpredictability of the prior art, a reasonable number of working embodiments would be required to enable the full breadth of the claim language. However, the specification fails to provide any suitable working examples.

Claim Breadth

The claim breadth is excessive and encompasses an inordinate number of HIV antigens, immunostimulatory CpG oligonucleotides, and adjuvants. However, the disclosure fails to provide sufficient guidance concerning all of these parameters.

¹ Haynes, B. F., 1996, HIV vaccines: where we are and where we are going, *The Lancet* 348:933-937.

² Piguet, V., et al., 2001, Living in oblivion : HIV immune evasion, *Sem. Immunol.* 13:51-57.

³ Staprans, S. I., et al., 2004, The roles of nonhuman primates in the preclinical evaluation of candidate AIDS vaccines, *Expert Rev. Vaccines* 3(4):S5-S32.

⁴ Gallo, R. C., 2005, The end of the beginning of the drive to an HIV-preventive vaccine: a view from over 20 years, *The Lancet* 366:1894-1898.

Lack of Guidance

As noted *supra*, the disclosure fails to provide sufficient guidance pertaining to suitable immunogens, adjuvants, and vaccine regimens that will lead to a protective immune response. The disclosure fails to provide any guidance pertaining to the correlates of human protection. Thus, the skilled artisan cannot reasonably predict *a priori* which combination of immunogen, adjuvant, and ISS will lead to the desired immune response.

Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 15, 16, 21, and 22 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Deml et al. (1999).⁵ Deml and colleagues provide compositions comprising an HIV antigen (e.g., gp160), immunostimulatory CpG oligonucleotide,

⁵ Deml, L., et al., 1999, Immunostimulatory CpG motifs trigger a T helper-1 immune response to human immunodeficiency virus type-1 (HIV-1) gp160 envelope proteins, Clin. Chem. Lab. Med. 37(3):199-204.

and adjuvant (e.g., Alum). This teaching meets all of the claimed limitations.

35 U.S.C. § 103(a)

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 17, 18, and 20 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Deml et al. (1999) in view of Bruck

et al. (1999).⁶ As set forth *supra*, Deml and colleagues provide compositions comprising an HIV antigen (e.g., gp160), immunostimulatory CpG oligonucleotide, and adjuvant (e.g., Alum). This teaching does not disclose HIV-1 Nef-Tat fusion proteins, Protein D fusion partners, or the use of a saponin adjuvant. However, Bruck and associates provide vaccine compositions comprising HIV-1 Nef-Tat fusion proteins wherein said proteins are fused to a fusion partner such as Protein D, lipoprotein D, or fragments thereof. This teaching also discloses the use of saponins as a suitable adjuvant. Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute the HIV-1 gp160 immunogen of Deml and associates with the HIV-1 Nef-Tat fusion proteins provided by Bruck and colleagues. It would also have been *prima facie* to substitute the Alum adjuvant with a saponin adjuvant since this are both strong adjuvants. One of ordinary skill in the art would have been motivated to do so to generate high-titer immunological reagents against the Nef and Tat proteins.

Claims 23 and 24 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Deml et al. (1999) in view of Krieg et al. (2002).⁷ As set forth *supra*, Deml and colleagues provide compositions comprising an HIV antigen (e.g., gp160), immunostimulatory CpG oligonucleotide, and adjuvant (e.g., Alum). This teaching does not disclose CpG oligonucleotides comprising one phosphorothioate modification or the particular ISSs claimed. However, Krieg and associates provide vaccine

⁶ Bruck, C., et al., 1999, Fusion proteins comprising HIV-1 Tat and/or Nef proteins, WO 99/16884.

⁷ Krieg, A. M., et al., 2002, Immunostimulatory nucleic acid molecules for activating dendritic cells, U.S. Patent No. 6,429,199 B1.

compositions comprising CpG oligonucleotides carrying phosphorothioate modifications and the same ISSs currently claimed. Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute the CpG ISSs of Deml and associates with phosphorothioate-modified CpG ISSs having the specified sequences because this would increase the stability of the oligonucleotide.

The following prior art, which was not relied upon in the office action, is considered germane to applicant's disclosure:

- Krieg, A. M., et al., 2001, Immunostimulatory nucleic acid molecules, U.S. Patent No. 6,239,116 B1.
- Davis, H. L., et al., 2002, Use of nucleic acids containing unmethylated CpG dinucleotide as an adjuvant, U.S. Patent No. 6,406,705 B1.
- Kensil, C. A., 2006, Compositions of CpG and saponin adjuvants and uses thereof, U.S. Patent No. 7,049,302 B1.

Correspondence

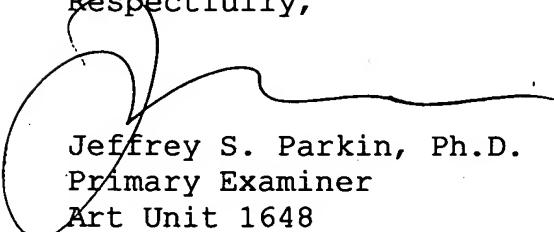
Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 10:30 AM to 9:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Bruce R. Campell, Ph.D., can be reached at (571) 272-0974. Direct general status inquiries to the Technology Center 1600 receptionist at (571) 272-1600. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

Applicants are reminded that the United States Patent and Trademark Office (Office) requires most patent related correspondence to be: a) faxed to the Central FAX number (571-273-8300) (updated as of July 15, 2005), b) hand carried or delivered to the Customer Service Window (now located at the

Randolph Building, 401 Dulany Street, Alexandria, VA 22314), c) mailed to the mailing address set forth in 37 C.F.R. § 1.1 (e.g., P.O. Box 1450, Alexandria, VA 22313-1450), or d) transmitted to the Office using the Office's Electronic Filing System. This notice replaces all prior Office notices specifying a specific fax number or hand carry address for certain patent related correspondence. For further information refer to the Updated Notice of Centralized Delivery and Facsimile Transmission Policy for Patent Related Correspondence, and Exceptions Thereto, 1292 Off. Gaz. Pat. Office 186 (March 29, 2005).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,



Jeffrey S. Parkin, Ph.D.
Primary Examiner
Art Unit 1648

12 November, 2006